

## PATENT COOPERATION TREATY

## PCT

(2)

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 17554 - WO - 04	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IL2005/000358	International filing date (day/month/year) 30/03/2005	(Earliest) Priority Date (day/month/year) 30/03/2004
Applicant VISSUM RESEARCH DEVELOPMENT COMPANY ...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b.  With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2.  Certain claims were found unsearchable (See Box II).

3.  Unity of Invention is lacking (see Box III).

## 4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

BI-SPECIFIC ANTIBODIES FOR TARGETING CELLS INVOLVED IN ALLERGIC-TYPE REACTIONS,

## COMPOSITIONS AND USES THEREOF

## 5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

b.  none of the figures is to be published with the abstract.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IL2005/000358

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: **36-41** because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 36-41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

## Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IL2005/000358A. CLASSIFICATION OF SUBJECT MATTER  
C07K16/28 C07K16/42 A61K39/395 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTT V L ET AL: "Activating and inhibitory signaling in mast cells: new opportunities for therapeutic intervention?" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 106, no. 3, September 2000 (2000-09), pages 429-440, XP002295990 ISSN: 0091-6749 page 434, left-hand column, paragraph 3 page 434, right-hand column, lines 34-37 page 429, right-hand column, lines 12-14 Concluding remarks ----- WO 03/064662 A (TANOX, INC) 7 August 2003 (2003-08-07) page 2, line 20 - page 4, line 10 examples 2-4 ----- -/-	1-41
X		1-41

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \*Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

25 January 2006

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Authorized officer

COVONE-VAN HEES, M

## INTERNATIONAL SEARCH REPORT

International Application No PCT/IL2005/000358
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/030835 A (SCHERING CORPORATION) 17 April 2003 (2003-04-17) page 3, columns 10-18 examples -----	1-41
A	BIASSONI R ET AL: "Human natural killer cell receptors: insights into their molecular function and structure" JOURNAL OF CELLULAR AND MOLECULAR MEDICINE, vol. 7, no. 4, October 2003 (2003-10), pages 376-387, XP002364094 ISSN: 1582-1838 page 381, right-hand column, last line - page 382, left-hand column, last line -----	1-41
A	CANTONI CLAUDIA ET AL: "Molecular and functional characterization of IRp60, a member of the immunoglobulin superfamily that functions as an inhibitory receptor in human NK cells" EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 29, no. 10, October 1999 (1999-10), pages 3148-3159, XP002364095 ISSN: 0014-2980 cited in the application the whole document -----	1-41
T	BACHELET I ET AL: "IRp60 modulates an array of human mast cell functions" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 115, no. 2, February 2005 (2005-02), page S206, XP004845981 ISSN: 0091-6749 abstract -----	1-41
T	BACHELET I. ET AL.: "THE INHIBITORY RECEPTOR IRP60 (CD300a) IS EXPRESSED AND FUNCTIONAL ON HUMAN MAST CELLS" J.OF IMMUNOLOGY, [Online] vol. 75, no. 12, December 2005 (2005-12), pages 7989-7995, XP002364096 the whole document -----	1-41
T	MUNITZ A. ET AL.: "THE INHIBITORY RECEPTOR IRP60 (CD300a) SUPPRESS THE EFFECTS OF IL-5, GM-CSF AND EOTAXIN ON HUMAN PERIPHERAL BLOOD EOSINOPHILS" BLOOD, [Online] XP002364097 DOI 10.1182/blood-2005-07-2926 -----	1-41
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IL2005/000358

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>DATABASE PUBMED [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; February 2005 (2005-02), F.LEVI-SCHAFFER ET AL.: "IGE ACTIVATION OF MAST CELLS: THE BEGINNING OF THE END OR THE END OF THE BEGINNING?" XP002364099 retrieved from INTERNET accession no. <a href="http://www.mastcells.org/lecture%20abstracts.htm">http://www.mastcells.org/lecture%20abstracts.htm</a> abstract -----</p>	1-41

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IL2005/000358

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03064662	A 07-08-2003	NONE	
WO 03030835	A 17-04-2003	CA 2462883 A1 EP 1439857 A2 MX PA04003291 A	17-04-2003 28-07-2004 23-07-2004

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/IL2005/000358**Cover sheet (examiner version, for internal use only)**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IL2005/000358	30.03.2005	30.03.2004

International Patent Classification (IPC) or both national Classification and IPC

C07K16/28, C07K16/42, A61K39/395, A61P37/08

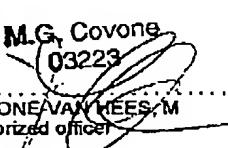
## Applicant

YISSUM RESEARCH DEVELOPMENT COMPANY ...

## 1. This report contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

M.G. Covone  
03223  
COVONE/VAN HEES, M  
Authorized officer



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/IL2005/000358**Box No. I Basis of the opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - a sequence listing
    - table(s) related to the sequence listing
  - b. format of material:
    - in written format
    - in computer readable form
  - c. time of filing/furnishing:
    - contained in the international application as filed.
    - filed together with the international application in computer readable form.
    - furnished subsequently to this Authority for the purposes of search.
3.  In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**Box No. II Priority**

1.  The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2.  This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITYInternational application No.  
PCT/IL2005/000358

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,  
 claims Nos. 36-41 (as to IA)

because:

the said international application, or the said claims Nos. 36-41 (as to IA) relate to the following subject matter which does not require an international preliminary examination (specify):  
see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the whole application or for said claims Nos.

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished  
 does not comply with the standard

the computer readable form

has not been furnished  
 does not comply with the standard

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/IL2005/000358**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or  
industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	1-41
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-41
Industrial applicability (IA)	Yes: Claims	1-35
	No: Claims	

**2. Citations and explanations**

see separate sheet

**Box No. VII Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

see separate sheet

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

**PCT/IL2005/000358**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 36-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1 Reference is made to the following documents:

- D1: Ott VL et al. (2000)
- D2: WO03064662
- D3: WO03030835

2 **Novelty (Article 33(2) PCT)**

- 2.1 The documents D1-D3 are regarded as being the closest prior art to the subject-matter of independent claims 1,12-14,18,19,26-28,34,36-41.
- 2.2 D1 reviews the coaggregation of inhibitory receptors (ITIM) e.g. Fc $\gamma$ RIIB, gp49 and activating receptors (ITAM) e.g. Fc $\epsilon$ RI on mast cells as a possible therapeutic target for atopic diseases and allergies (see pg.430 left-hand column 3rd paragraph; "concluding remarks). Coaggregation of gp49 and Fc $\epsilon$ RI inhibits mast cells activation (see pg.434 right-hand column I.34-37). IL-5 contributes in recruiting eosinophils during allergic reactions (see pg.429 right-hand column I.12-14).
- 2.3 D2 studies the cross-linking of Fc $\epsilon$ RI (ITAM) and HM18 (mouse equivalent gp49) or Fc $\gamma$ RII (ITIM) with bispecific antibodies to treat allergies (see pg.2 I.20 - pg.4 I.10; ex.2-4).
- 2.4 D3 teaches also the cross-linking of ITAM and ITIM to treat e.g. asthma. Several ITAM-ITIM combination are suggested (see pg.3 I.10-18; examples).

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

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2.5 None of the available prior art documents however mention a bispecific complex for targeting the ITAM IRp60. Consequently the subject-matter of claims 1-41 appears to be novel (Article 33(2) PCT).

**3 Inventive Step (Article 33(3) PCT)**

3.1 Document D1-D3, are considered to represent the most relevant state of the art, whereby all three documents (see point 2.2-2.4) discloses the concept of cross-linking activating and inhibitory receptors in order to inhibit mast cells activation. D1 moreover also identifies eosinophils to be involved in the allergic response.

3.2 The problem to be solved by the present invention may be regarded as providing a bispecific antibody targeting an alternative ITAM on target cells (mast cells or eosinophils).

3.3 The solution to this problem proposed in claim 1 of the present application, namely to target IRp60, is considered as not involving an inventive step (Article 33(3) PCT) since IRp60 appears to be equivalent to the ITAM chosen in D2 or D3 not leading to any surprising effect or advantages.

3.4 The same is valid, mutatis mutandis for the subject-matter of independent claims 12-14,18,19,26-28,34,36-41, which are therefore also not inventive (Article 33(3) PCT)

3.5 The dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, since they are obvious alternatives for a person skilled in the art in this technical field not leading to any surprising effect.

4 For the assessment of the present claims 36-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IL2005/000358

**Re Item VII**

**Certain defects in the international application**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

**Re Item VIII**

**Certain observations on the international application**

- 4.1 Claim 1 lacks clarity and is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and examples. Present claim refers to generic "target cells". On one hand this term is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT. On the other hand the application exemplifies only mast cells and eosinophils and no generalization is envisaged (no support Article 6 PCT).
- 4.2 The term "bi-specific complex" used throughout the set of claims has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.
- 4.3 The term "homologues thereof" used e.g in claims 1, 12 etc. is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.
- 4.4 The applicant is should check the incorrect dependency in claim 25 (reads 10 to 15 should be 16-20), claim 34 (reads 27 should be 34), claim 38 (reads 1-17 should be 1-15).